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AWARD NUMBER: W81XWH-04-1-0490

TITLE: Polychlorinated Biphenyls, Organochlorines & PD Risk: A Case Control Study
in Alaska

PRINCIPAL INVESTIGATOR: Caroline M. Tanner, M.D., Ph.D.

CONTRACTING ORGANIZATION: Parkinson's Institute
Sunnyvale, California 94089-1605

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Fort Detrick, Maryland 21702-5012

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14. ABSTRACT The intent of this research is to conduct a case control study of Parkinson's Disease (PD) among Alaska Natives to determine the association of exposure to polychlorinated biphenyl (PCBs) residues, organochlorine pesticides and methylmercury with PD. The hypothesis is that increased exposure to these compounds will be associated with an increased risk of PD. Exposure will be determine by direct measurement of serum levels, as these compounds are persistent in body tissues. In addition, lifelong exposure will be estimated by structured interview, including a dietary history with specific attention to intake of fish, marine mammals and wild game, known sources of bioconcentration of these environmentally persistent compounds. The project will be conducted in two phases. Phase 1 is a developmental period and is currently ongoing. During this time, the specific aspects of the study design are being established, detailed protocols are being developed, and the necessary approvals for the research are being obtained. Once Phase 1 is complete, Phase 2 will be initiated. During Phase 2 the study will be conducted.					
15. SUBJECT TERMS Parkinson's disease, polychlorinated biphenyl, organochlorine pesticides, methylmercury, Alaska natives, neurodegeneration					
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Table of Contents

Table of Contents.....	3
Introduction.....	4
Body.....	4
Key Research Accomplishments.....	7
Reportable Outcomes.....	7
Conclusion.....	7
References.....	7
Appendices.....	7

A. Introduction

The intent of this proposal is to conduct a case control study of Parkinson's disease (PD) among Alaska Natives to determine the association of exposure to polychlorinated biphenyl (PCBs) residues, organochlorine pesticides and methylmercury with PD. The hypothesis is that increased exposure to these compounds will be associated with an increased risk of PD. Exposure will be determined by direct measurement of serum levels, as these compounds are persistent in body tissues. In addition, lifelong exposure will be estimated by structured interview, including a dietary history with specific attention to intake of fish, marine mammals and wild game, known sources of bioconcentration of these environmentally persistent compounds. The project will be conducted in two phases. Phase 1 is a developmental period and is currently ongoing. During this time, the specific aspects of the study design are being established, detailed protocols are being developed, and the necessary Institutional Review Board (IRB) approvals for the research are being obtained. During Phase 2 the study will be conducted. Phase 2 will be initiated following completion of Phase 1.

B. Body

SCOPE OF WORK - PHASE 1

Task 1: Develop an ascertainment protocol using Indian Health Service (IHS) provider databases as the primary source, and identifying other possible sources of cases.

Task 2: Develop methods for identifying matched controls.

Accomplishments:

Since the last reporting period, study personnel traveled to AK 3 times to meet with collaborating neurologists to refine case ascertainment methods. Additionally, we met local investigators working on projects with potentially similar ascertainment methods to those being developed in this study. For example, the Alaska Area Diabetes program already developed methods for identifying diabetes cases using the Resource and Patient Management System (RPMS). The RPMS database will be our primary resource for identifying cases as well.

Methods for identifying matched controls were further explored and defined with input from the local review boards.

Lastly, study personnel attended the Alaska Native Health Research Conference 2006. The conference focused on describing on going health research in Alaska, preferred study methods utilized within Alaska Native/American Indian populations and health disparities.

Task 3: Develop a preliminary proposal for review by Native Alaska leaders. Subsequent detailed versions of the protocol will be submitted for review in accordance with protocol.

Accomplishments:

The study protocol, data collection instruments, and informed consents have gone through several iterations with input from collaborators in Alaska and Alaska Area IRB staff. The proposal has now been submitted to 2 Alaska Native health corporations in Anchorage, SouthCentral Foundation (SCF) and Alaska Native Tribal Health Consortium (ANTHC), both have Alaska Native leader representation. SCF recently approved the protocol. After addressing

resource utilization concerns within the Alaska Native Medical Center (ANMC), ANTHC has recommended the proposal for approval to their Board of Directors. Final approval from their Board of Directors is pending. If this is granted, all necessary approvals from the Alaska collaborators will be in place. This will allow us to obtain final approval from the Parkinson's Institute and U.S. Army IRBs.

Task 4: Establishing appropriate infrastructure and personnel in Alaska. This will include a physician/neurologist, project manager and local contacts within each tribal group. In addition, preliminary training in epidemiologic research methods may be a necessary part of a feasibility assessment.

Accomplishments:

We continue to work with 2 neurologists, Drs. Trimble and Gordon, to collaborate in the ascertainment and neurologic evaluations of cases. We hired an Alaska based research coordinator in July 2005 (although she subsequently left the position in January 2006 due to health problems.) Because of continuing delays in the Alaska IRB process and in an effort to preserve funds until we have final human subject approval, we have refrained from hiring any additional staff. However, we just renewed our effort to recruit AK based staff, since there is optimism that we may receive human subject approval and be able to begin subject recruitment by fall of 2006.

Task 5: Develop study instruments and a detailed protocol.

Accomplishments:

We developed study instruments for collecting detailed life histories with special focus on exposures through diet, place of residence, and occupational exposures. These were revised throughout the past year with input from and at the request of the Alaska Area IRB. Piloting of the questionnaires within the Alaska Native population is pending final IRB approval.

With advice from the Director of the Alaska Area Specimen Bank, we developed a draft specimen protocol as required by the Alaska Area IRB.

We identified the potential laboratories needed to conduct the PCB, Organochlorine and methylmercury analyses. Development of protocols for determining body burden of PCBs, organochlorine pesticides and methylmercury is ongoing.

Task 6: Refining the study protocol and preparing the operations manual.

Accomplishments:

Refining of the protocols is on going as we continue to receive input from the review boards in Alaska. The Alaska based research coordinator, who was also an Alaska Native, worked to revise the instruments to make them more culturally appropriate. The preparation of operations manuals is ongoing.

Task 7: IRB approval of final protocols.

Accomplishments:

This has been a challenging and rigorous task. There have been many unexpected delays in achieving approval to conduct this work in a native population. Final IRB approval is still

pending (see Table 1). We have approval in principle from Western Institutional Review Board (WIRB), the IRB representing the Parkinson's Institute. Final approval by WIRB is pending approval from all review boards representing the Alaska Native Medical System (AK Area IRB, SCF, and ANTHC).

After 1 year of review and iterations, the AK Area IRB approved the study in March 2006. This IRB was very satisfied with the quality of the protocol, and determined to use it as a prototype for the future. We also recently obtained approval from SCF. The ANTHC Abstracts Manuscripts and Protocols Review Committee (AMP RC) recommended the projects for approval to their Board of Directors. The proposal had been submitted and we await approval from the ANTHC Board of Directors (expected June 2006).

Approval from the University of CA, San Francisco Committee on Human Research (Dr. M. Lee) , was obtained in 2004. The submissions to the Veteran Affairs Pacific Islands Health Care System and resubmission to WIRB are currently being prepared. Because Dr. Ross's involvement involves contact with research participants, we elected to wait until the primary approvals from the Alaska Area IRB were in place, in order to avoid revisions.

Upon approval by all of the above, we will submit all certificates of approval to the US Army Office of Research Protections. After their review and approval, we will be allowed to recruit subjects at the ANMC. As the study expands to other regions of Alaska, we will seek approval by Native Health Corporations in those regions. Submissions to regional corporations are currently being prepared.

Table 1. Human Subject Approval Status

Institution	Review Board	Status	Approval Date
Parkinson's Institute	WIRB	Pending	
ANMC	AK Area IRB	Approved	12/20/2006
ANMC	ANTHC – AMP RC	Approved	4/25/2006
ANMC	ANTHC - Board of Directors	submitted	
ANMC	SCF	Approved	4/11/2006
AK Statewide	Native Corporations as necessary	not submitted	
PHRI	VA Pacific Islands Health Care System	not submitted	
US Army	Office of Research Protections (Army)	Pending	
UCSF	UCSF Committee on Human Research	Approved	9/7/2006
ANMC	Alaska Native Medical Center		
PHRI	Pacific Health Research Institute		
UCSF	University of California San Francisco		
WIRB	Western Institutional Review Board		
ANTHC AMP RC	Alaska Native Tribal Health Consortium Abstracts, Manuscripts and Proposals Review Committee		
SCF	SouthCentral Foundation		

SCOPE OF WORK - PHASE 2

Initiation of phase 2, the conduct of the study, is pending final IRB approvals.

C. Key Research Accomplishments

- Met with collaborating neurologists in AK and other local investigators to develop potential methods of case and control ascertainment.
- Extensive meetings with Alaska review board representatives to satisfy the requests of board members.
- Revisions to study instruments, consents, and protocols to make more culturally appropriate and satisfy the requests of the many reviewers.
- Human subjects approval was obtained by many of the required review boards (see Table 1).

D. Reportable Outcomes

While many milestones of phase 1 of this study were met, we are still in the process of obtaining IRB approvals necessary to begin study conduct. Until this has been accomplished and study conduct finished, we will not have reportable outcomes.

E. Conclusions

Phase 1 of this study is well underway. We anticipate having the appropriate IRB approvals and beginning study conduct (Phase 2) by fall 2006. Following the completion of subject enrollment, data and sample collection, and analysis, it will be possible to draw relevant scientific conclusions.

F. References

None

G. Appendices

Copies of current human subject approvals are enclosed:

- WIRB (approval in principal)
- AK Area IRB
- SCF
- ANTHC AMP RC (recommended for approval)
- UCSF

WIRB[®]
WESTERN INSTITUTIONAL REVIEW BOARD[®]
WESTERN INTERNATIONAL REVIEW BOARD[®]
3535 SEVENTH AVENUE, SW • OLYMPIA, WA 98502-5010
P.O. BOX 12029 • OLYMPIA, WA 98508-2029
(360) 252-2500 • 1-800-562-4789 • FAX (360) 252-2498

October 28, 2004

Caroline M. Tanner, M.D., Ph.D.
The Parkinson's Institute
1170 Morse Avenue
Sunnyvale, CA 94089-1605

Dear Dr. Tanner:

SUBJECT: BOARD ACTION: APPROVAL IN PRINCIPLE
U.S. Army Medical Research Acquisitions Activity
Protocol #W23RYX-4007-N601
WIRB #20041208/1060268

At the meeting of October 18, 2004, Western Institutional Review Board (WIRB) reconsidered the above-referenced research. The purpose of this letter is to inform you of the action taken by the Board.

WIRB voted to designate this research as "approved in principle." This designation indicates that the Board believes the research as currently drafted has the potential to be suitable for IRB approval upon completion.

The Board understands that this research is in the developmental stage and will still need to undergo review by a number of IRBs and tribal corporations in Alaska. The Board also understands that the research as presented to WIRB is likely to change based on the requirements by the other reviewing bodies, and the final protocol, and other study materials will be submitted for further WIRB review.

The Board did not review the submitted consent form, but instead recommends that it be reviewed by the other reviewing bodies first and the results submitted to WIRB for review. The Board also expects that the changes required by the Board to a number of research materials when it initially tabled the research will be reflected in the revised documents to be submitted for review.

This letter does not signify approval of the research, and no research activities may be initiated on the basis of this letter. **No research activities can commence until the Board has reviewed and approved the final grant, protocol, and other study materials.** Please reference the WIRB protocol number when submitting the final documents.

You may address WIRB in person or in writing regarding its actions. If you wish to address the Board in person or if you have questions, please contact WIRB Director of Regulatory Affairs, Greg Lim, at 360-252-2493.

Sincerely,

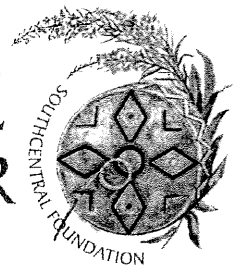
A handwritten signature in black ink, reading "Theodore D. Schultz". The signature is written in a cursive style with a large, stylized 'T' and 'S'.

Theodore D. Schultz, J.D.
Chairman

TDS:GL:slh
W:\Documents\Correspondence\Board Requirements\Tanner 20041208
cc Carl G. Hover, U.S. Army Medical Research Acquisitions Activity
Monica Korell, The Parkinson's Institute
Dr. Richard W. Seaman, WIRB Panel Seven Chair
Protocol File – Work Order 1-279279-1
Study File



ALASKA NATIVE MEDICAL CENTER



January 31, 2006

Caroline M. Tanner, MD, PhD
Brian Trimble, MD
The Parkinson's Institute
1170 Morse Avenue
Sunnyvale, CA 94089

Dear Dr. Tanner and Dr. Trimble,
During the November and December 2005 meetings the Alaska Area Institutional Review Board (IRB) reviewed and approved your proposal **2005-04-005 Polychlorinated Biphenyls, Organochlorines and Parkinson's Disease Risk: A Case Control Study in Alaska Natives** with the following contingencies:

1. The Alaska Area Institutional Review Board (AAIRB) requires that the recruitment of participants to the research protocol be conducted by persons that are **not** part of the clinical care team.
2. The researchers are bound by The Specimen Banking Protocol and any future testing of the collected specimen must be reviewed by the AAIRB prior to use.
3. Modify the consent forms to add contact information for the Alaska Area IRB Administrator, telephone (907) 729-3924.

Prior to making any changes to the consent form or protocol you must receive approval from the Alaska Area IRB. Request our annual renewal forms from the IRB Administrator at least six weeks prior to the protocol expiration date. Please ensure that project renewal information is complete and submitted to the IRB Administrator at least four weeks prior to expiration. The annual renewal information should include but not be limited to a one page abstract of the research, the Alaska Area IRB annual renewal form, a current copy of the consent/assent forms, a cover letter signed by the PI to the IRB with a project summary and an electronic copy of all items to be sent to the IRB members. The submission date for the monthly IRB meeting is the first day of each month. Inform the IRB by letter when the protocol is complete/closed.

As a reminder, the IRB must review and approve all human subjects' research protocols at intervals appropriate to the degree of risk but no less than once per year. Per 45 CFR 46.109(e) there is no grace period beyond one year from the last IRB approval date. It is your responsibility as the Principal Investigator (PI) to maintain approval status for your project by tracking, renewing and obtaining IRB approval for all modifications to the protocol and the consent/assent form. Keep this approval in your protocol file as proof of IRB approval and as a reminder of the expiration date. To avoid lapses in approval of your research which will result in suspension of participant

enrollment and/or termination of the protocol submit the continuation request at least four weeks prior to the expiration date of December 20, 2006.

All research approved by the Alaska Area IRB is subject to 45 CFR 46 "Protection of Human Subjects" regulations. Investigators are expected to be familiar with these provisions and adhere strictly to all requirements. You are required to have all personnel involved in the research complete the training at www.citiprogram.org. Please retain your completion certificates from the Collaborative IRB Training Institute (CITI) for a period of 36 months.

After IRB approval is obtained all research involving staff, patients, or resources at the Alaska Native Medical Center (ANMC) must be submitted to the Board(s) of directors of ANMC's parent organization(s), Southcentral Foundation and the Alaska Native Tribal Health Consortium. Your points of contact at Alaska Native Tribal Health Consortium and Southcentral Foundation are Dr. Anne Lanier and Dr. Ruth Etzel at aplanier@anthc.org and raetzel@scf.cc. Please send your proposal and a copy of the IRB approval letter to both Dr. Etzel and Dr. Lanier.

Before submitting any manuscripts, reports, or abstracts for consideration for publication or presentation, Board of Directors review must be obtained. To ensure timely review please send an electronic copy of these items to both Dr. Etzel and Dr. Lanier at least 8 weeks before the deadline for submission.

You can contact me at tjpowell@anmc.org or call (907) 729-3924 between the hours of 8:00 am and 4:00 pm, Monday through Friday.

Sincerely,



Terry J. M. Powell
IRB Administrator
Alaska Area Institutional Review Board

Southcentral Foundation

April 11, 2006

Caroline M. Tanner, MD, PhD, Director of Clinical Research
The Parkinson's Institute
1170 Morse Ave.
Sunnyvale, CA 94089

Dear Dr. Tanner:

The proposal entitled "Polychlorinated Biphenyls, Organochlorines and Parkinson's Disease Risk: A Case Control Study in Alaska Native People" was reviewed by the Southcentral Foundation (SCF) Board of Directors on April 11, 2006.

We have approved this proposal with the understanding that you will abide by the standard stipulations outlined in the enclosed Research Agreement. Please sign and return it to me at your earliest convenience.

This research project may begin as soon as SCF receives the signed Research Agreement from you. If you have any questions about these stipulations, please contact me at 729-5471.

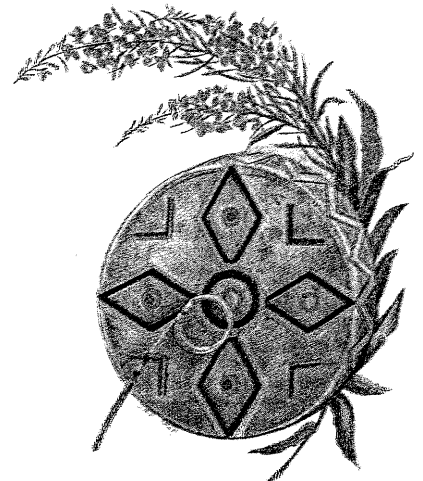
Sincerely yours,

SOUTHCENTRAL FOUNDATION



Ruth A. Etzel, M.D., Ph.D.
Medical Director Research

4501 Diplomacy Drive • Anchorage, Alaska 99508
(907) 729-4955 • Fax (907) 729-5000



Cortese, Katey

From: Korell, Monica
Sent: Monday, May 01, 2006 9:48 AM
To: Cortese, Katey
Subject: ANTHC AMP Review Committee recommendation for approval

From: Ferucci, Elizabeth D [mailto:EDFerucci@anmc.org]
Sent: Tuesday, April 25, 2006 10:26 AM
To: Korell, Monica
Cc: Etzel, Ruth A; Lanier, Anne P
Subject: RE: UPDATE: proposal status

Dear Monica,

I'm sorry for the delayed notification, but Dr. Trimble and I sat down with the clinic director and it appears that space will not be an issue. This information was brought back to ANMC's AMP Committee and the proposal was recommended for approval today. The next ANTHC Board of Directors meeting is June 14-15, and the study will go before the board on that date. Once that review is complete, the ANTHC approval process will be done.

Dr. Etzel can give you more information regarding timing of SCF review.

Thanks,

Liz

Elizabeth D. Ferucci, MD
Medical Research Associate
Office of Alaska Native Health Research
Alaska Native Tribal Health Consortium
Phone 907-729-4591
Fax 907-729-2924
edferucci@anmc.org

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Version: 7.1.385 / Virus Database: 268.5.1/327 - Release Date: 4/28/2006

5/1/2006

Committee on Human Research
Project Summary Sheet
CHR: H6442-25720-02

Study Title

Polychlorinated Biphenyls, Organochlorines and Parkinson's Disease Risk: A Case Control Study in Alaska Natives

Principal Investigator

Marion M. Lee Title: Professor
Department: Epidemiology & Biostatistics
Phone: 476-0743 Fax: E-Mail: mmlee@itsa.ucsf.edu
Address: Box 0560

Contacts

<u>Name</u>	<u>Position</u>	<u>Box</u>	<u>Phone</u>	<u>E-Mail</u>
Etkin, Coral	Former Contact	0560	476-8945	etkin@epi.ucsf.edu
Lee, Marion M.	PI	0560	476-0743	mmlee@itsa.ucsf.edu

Human Subjects Training

The PI and Co-PI must complete the UCSF online training course: Protecting Human Research Subjects

<u>Name</u>	<u>Last Completed</u>
Lee, Marion M.	9/16/04

Review Details

<u>Approval Number</u>	<u>Status</u>	<u>Received</u>	<u>Reviewed</u>	<u>Approved</u>	<u>Expires</u>
H6442-25720-02	Approved	8/5/2005	8/26/2005	8/26/2005	9/7/2006
H6442-25720-01	Approved	8/19/2004	9/7/2004	9/7/2004	9/7/2005

Attachments:

Special Study Information

Site: Campus

Other

Populations:

How many subjects will be enrolled here: 200

Will subjects be paid: Yes

Drugs and Devices

Name

IND/IDE No.

Funding

Agency / Sponsor Name

Award No.

Type

Funded

DOD

Yes

FederalWide Assurances

The CHR is the Institutional Review Board (IRB) for UCSF and its affiliates. The institutional FederalWide Assurance (FWA) numbers are listed below. Not all of the following FWA numbers apply to this study.

Institution

FWA #

UCSF

00000068

Ernst Gallo Clinical and Research Center (EGCRC)

00000304

J. David Gladstone Foundation

00000087

Northern California Institute for Research and Education (NCIRE)

00000256

San Francisco department of Public Health (SFDPH)

00000162

San Francisco General Hospital (SFGH)

00000315

Veterans Affairs Medical Center (VAMC)

00000280